claims 27, 29, 30, and 37-39, and withdrew claims 31-36 from consideration as being drawn to a nonelected invention. Claims 30-36 have been cancelled. Thus, claims 27, 29 and 37-39 are pending.

Claims 27 and 29 have been amended to more clearly claim the invention. The amendment is supported by the specification at, for example, page 14, lines 10-13, and page 15, line 1 to page 17, line 22. No new matter is added by this amendment.

In paragraph 17 of Paper No. 9, the Examiner stated that applicants had not updated the status of U.S. Application Serial No. 07/593,271. The status has been updated by this amendment.

In paragraph 18, the Examiner objected to the title of the invention. The new title suggested by the Examiner has been adopted by this amendment.

In paragraph 20, the Examiner rejected claim 30 under 35 U.S.C. § 102(b) as being clearly anticipated by Sullivan et al. Applicants respectfully traverse this rejection, which is now moot, as claim 30 has been cancelled without prejudice or disclaimer.

In paragraphs 21-22, the Examiner rejected claims 27, 29 and 37-39 under 35 U.S.C. § 103 over Sullivan et al. in view of Coulter et al. and Smith et al. Applicants respectfully traverse this rejection for the reasons stated below.

RESPONSE TO THE § 103 REJECTION

The Examiner's § 103 rejection can be summarized as follows. Sullivan is cited for teaching a method for purifying whole

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

polyvalent antivenin antibodies. Coulter is cited for teaching a method for producing F(ab) antibody fragments. Smith is cited for teaching "the advantages of F(ab) fragments for the neutralization and clearance of toxic substances in therapeutic applications." The Examiner suggests that one skilled in the art would have been motivated to combine these references because Smith discloses that F(ab) is cleared more rapidly than intact IgG and is less immunogenic than IgG. The Examiner suggests further that a purified F(ab) antivenin would have been expected to be successful in light of these teachings.

Applicants first question whether Smith's use of F(ab) fragments to clear digoxin would have motivated one skilled in the art to make a F(ab) fragment to treat snake venom poisoning. Smith's F(ab) fragment clears digoxin more rapidly than intact antibody because the F(ab)-digoxin complex is small enough to be excreted through the kidney. This property is one of the principal reasons that Smith and his colleagues chose F(ab) fragments over intact antibody, as explained below:

> The intact antibody-digoxin complex was too large to enter the glomerular filtrate, resulting in prolonged elevation of plasma digoxin levels and rising concerns about the possibility of recurrent digoxin toxicity as the heterologous antibody population was degraded. . . . The Fab fragment-digoxin complex is small enough to allow rapid clearance.

Zucker et al., "Fab Fragments of Digoxin-Specific Antibodies Used to Reverse Ventricular Fibrillation Induced by Digoxin Ingestion in a Child," Pediatrics, vol. 70, no. 3, pp. 468-471 (1982) (Exhibit 1). The F(ab)-digoxin complex is relatively small

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

because the molecular weight of digoxin (781 daltons) does not add substantially to the molecular weight of the F(ab) fragment (50,000 daltons). Venoms, however, comprise several proteins in the molecular weight range of 20,000 to 90,000 daltons and, when complexed with a F(ab) fragment, would be too large to be excreted rapidly by glomerular filtration (Exhibit 2, Smith Decl. ¶ 6). Thus, an expectation of more rapid clearance would not have motivated those skilled in the antivenin art to use F(ab) fragments.

Another reason Smith and his colleagues chose a F(ab) fragment over an intact antibody, as noted by the Examiner, was their expectation that the F(ab) fragment would be less antigenic than the parent IgG molecule. F(ab) fragments were expected to be less antigenic because they "lacked the antigenic determinants of the Fc fragments" present in intact antibody. Clin. Exp. Immunol., vol. 36 p. 385. At the time the invention was made, however, commercial antivenins included $F(ab)_2$ antibody preparations (Exhibit 2, Smith Decl. ¶ 7). Since $F(ab)_2$ fragments also lack the Fc portion of the antibody molecule, expectation of less antigenicity would not have motivated those skilled in the antivenin art to use a F(ab) fragment instead of a $F(ab)_2$.

Even if, however, the art cited by the Examiner would have suggested to one skilled in the antivenin art to try a F(ab) fragment, the differences between digoxin and snake venoms would have made it impossible to predict whether a F(ab) would work. F(ab) fragments have been used infrequently as therapeutic agents,

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

in part because rapid clearance can be a disadvantage, as Smith recognized:

> Little attention has been directed toward heterologous Fab fragments as therapeutic agents in immune deficiency states, presumably because their clearance from the body has generally been considered too rapid to be clinically useful.

Clin. Exp. Immunol., vol. 36, p. 393. Despite Smith's success using F(ab) fragments to treat digoxin overdose, rapid clearance would have remained a concern for F(ab) antivenins. Unlike digoxin which is ingested and dispersed in the bloodstream and interstitial fluid, snake venoms are injected into muscle or fatty areas and are slowly released from the site of the bite. Consequently, one skilled in the art would have been concerned that rapid clearance might cause the F(ab) fragment to clear too quickly to effectively neutralize later-released venom (Exhibit 2, Smith Decl. ¶ 8).

In addition, one skilled in the art could not have predicted whether the structural differences between F(ab) fragments, on the one hand, and $F(ab)_2$ fragments and intact antibody, on the other, are such that F(ab) fragments would not work. Unlike $F(ab)_2$ fragments and intact antibodies, which have two binding sites, F(ab) fragments have only a single binding site. As a result, F(ab) fragments cannot form cross-linked antibody-antigen complexes like $F(ab)_2$ fragments and intact antibodies or initiate complement fixation like such complexes. Formation of such complexes, however, is important to their removal by the reticuloendothelial system, where large complexes are cleared most quickly (Exhibit 2, Smith Decl. ¶ 9). Moreover, because F(ab)

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N.W.
WASHINGTON, DC 20005
1-202-408-4000

fragments are relatively small (compared to intact immunoglobulin and $F(ab)_2$ fragments) and the venom molecules are relatively large (compared to digoxin), one skilled in the art would have been concerned that a F(ab)-venom complex would retain toxicity (Exhibit 2, Smith Decl. ¶ 10). Thus, one could not have predicted whether F(ab) fragments would function like $F(ab)_2$ fragments or intact antibodies.

The unpredictability of using F(ab) fragments to treat snake venom toxicity is underscored by the failure of F(ab) fragments to treat another toxin-- α-amanitin, which causes mushroom poisoning. Relying on the success of immunotherapy in testing digoxin poisoning (just like the Examiner in the outstanding rejection), Faulstich et al. (Exhibit 3) found that similar approach using amatoxin-specific immunoproteins was unsuccessful, as summarized below:

> The present study was prompted by reports that high-affinity antibodies raised against digoxin were able to reverse the toxic effects of the drug in animals. Moreover, F(ab) fragments of the digoxin-specific antibodies were successfully employed in a case of human suicidal digoxin poisoning. Such beneficial effects were not observed with the amatoxin-specific immunoproteins.

(Exhibit 3, p. 497; citations omitted). Quite to the contrary, the toxicity of α-amanitin was 50-fold higher in mice given a F(ab) fragment than in controls (Exhibit 3, pp. 493-94).

The unpredictability of this field is further supported by Balthasar et al. (Exhibit 4), who used digoxin as a model drug for studying antidrug antibody fragments. These authors cited Faulstich's work (discussed above) as evidence of the "formidable

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

hurdles" that must be addressed in immunotherapy: "The risk of redistributing systemic toxicity, rather than minimizing systemic toxicity, should be appreciated as a potential outcome of the proposed approach." (Exhibit 4 at page 738, right column.) Thus, even in 1994, those of skill in the art of antibody therapy of toxicity continue to recognize the unpredictability of this field.

In short, before the present invention, one skilled in the art would not have predicted whether F(ab) antivenins would work. "Obvious to try" is not the test for obviousness under 35 U.S.C. § 103. Gillette Co. v. S.C. Johnson & Sons, Inc., 16 U.S.P.Q. 2d 1923 (Fed. Cir. 1990). The proper test is whether there would have been a "reasonable expectation" that F(ab) fragments would be successful antivenins. Amgen, Inc. v. Chugai Pharmaceuticals Co. Ltd., 18 U.S.P.Q. 1016 (Fed. Cir. 1991). Given the differences between digoxin and snake venoms -- differences which would have taught away from using F(ab) antivenins -- applicants submit that one skilled in the art could not have reasonably expected F(ab) antivenins to work.

Aside from the failure of the prior art to teach or suggest using F(ab) fragments as antivenins, however, the patentability of the present invention is affirmatively demonstrated by objective evidence of nonobviousness -- long-felt need and unexpected results.

A critical need for improved antivenins existed for many years before the present invention. Intact immunoglobulin and $F(ab)_2$ antivenins had been available since at least 1947 and 1969, respectively, and virtually no improvements has been made since

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

1969 despite deficiencies in these products (Exhibit 2, Smith Decl. ¶ 7). The deficiencies were so great that the British National Formulary 1974-76 (page 34), referring to the antivenin available to treat Vipera berus venom, suggested that "The bite is less dangerous than the antiserum." In this country, the FDA has recognized the current need for improved antivenins, as evidenced by its designation of the first purified F(ab) antivenin as an Orphan Drug (Exhibit 5). Moreover, in an effort to assist getting this product on the market as soon as possible, the FDA has provided financial support to the manufacturer to conduct clinical trials (Exhibit 6). Clearly, the FDA believes that the present invention is an important improvement over conventional intact antibody and $F(ab)_2$ antivenins. Such satisfaction of a long-felt need is persuasive evidence of nonobviousness. See In re Dow Chemical, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988) ("Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness").

Moreover, the purified F(ab) fragments of the present invention have been shown to be much more potent than conventional antivenin. More specifically, a purified ovine F(ab) antivenin has been compared to conventional antivenin in a recently completed clinical trial in Sweden (Exhibit 2, Smith Decl. ¶ 12). In this study, the efficacy of 100 or 200 mg of purified F(ab) antivenin was comparable to that obtained when using 1.4 g of a conventional $F(ab)_2$ product (Exhibit 2, Smith Decl. ¶ 13). Thus, efficacy was retained with a much reduced dose. Such improved potency is a significant benefit because lower dosages mean

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

reduced risk of an adverse immune reaction. Moreover, such an unexpected advantageous property is a well recognized basis for rebutting prima facie obviousness. See, e.g., In re Chupp, 2 U.S.P.Q. 2d 1437, 1439 (Fed. Cir. 1987) ("Evidence of unobvious or unexpected advantageous properties may rebut a prima facie case of obviousness").[1/]

In sum, the prior art does not establish motivation to combine the references cited by the Examiner. Even if motivation were present, however, one skilled in the art could not have predicted with a reasonable expectation of success, that F(ab) fragments would work as antivenins. The nonobviousness of the invention is confirmed by the long-felt need in the industry and the advantages of the invention -- advantages which an independent source, the FDA, has clearly recognized. Those advantages include the improved potency of purified F(ab) fragments.

For the foregoing reasons, applicants request reconsideration and withdrawal of the obviousness rejection.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request the timely allowance of the pending claims.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under

1/ See also In re Lunsford, 148 U.S.P.Q. 716 (C.C.P.A. 1966) and In re Carabateas, 149 U.S.P.Q. 44 (C.C.P.A. 1966), where improved potency overcame a showing of structural obviousness and rendered the invention patentable.

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N.W.
WASHINGTON, DC 20005
1-202-408-4000

37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER

By: Jane E. R. Potter
Reg. No. 33,332

Dated: January 17, 1995

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000